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Role of climate in the spread of shiga toxin-producing Escherichia coli infection among children

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(Article begins on next page)

1 **ROLE OF CLIMATE IN THE SPREAD OF SHIGA TOXIN-PRODUCING ESCHERICHIA**
2 **COLI INFECTION AMONG CHILDREN.**

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18 **ABSTRACT**

19 Hemolytic-uremic syndrome (HUS) is a rare disease mainly affecting children that develops as a
20 complication of Shiga toxin-producing *Escherichia coli* (STEC) infection. It is characterised by
21 acute kidney injury, platelet consumption, and the mechanical destruction of red blood cells
22 (hemolysis). In order to test the working hypothesis that the spread of the infection is influenced by
23 specific climatic conditions, we analysed all of the identified cases of infection occurring between
24 June 2010 and December 2013 in four provinces of Lombardy, Italy (Milano, Monza Brianza,
25 Varese and Brescia), in which a STEC surveillance system has been developed as part of a
26 preventive programme.

27 In the selected provinces were recorded in few days a great number of cases, clusters which are
28 unrelated for spatially distant or for the disease is caused by different STEC serotypes.

29 In order to investigate a common factor that favored the onset of infection we have analysed in
30 detail the weather conditions in the areas. The daily series of temperature, rain and relative humidity
31 were studied to show the common climate peculiarities while the correlation coefficient and the
32 Principal Component Analysis, PCA, were used to point out the meteorological variable, maximum
33 temperature, as the principal climate element in the onset of the infection.

34 The use of Distributed Lag Non-Linear Models, DLNM, and the climate indices characterising Heat
35 Waves, HW, has allowed to identify the weather conditions associated with STEC infection.

36 The study highlighted a close temporal correlation between STEC infection in children and the
37 number, duration and frequency of heat waves. In particular if maximum temperature is greater than
38 90th percentile, days classificate as very hot, for 3 or more consecutive days the risk of infection
39 increasing.

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41 **Keywords:** Hemolytic-uremic syndrome; weather conditions; temperature; epidemiology; children.

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45 **INTRODUCTION**

46 Shiga toxin-associated haemolytic-uremic syndrome (HUS) is a severe, systemic, life-threatening
47 thrombotic microangiopathy mainly affects children and characterised by platelet consumption,
48 mechanical non-immune-mediated hemolysis, and multi-organ damage particularly affecting the
49 kidneys. It is endemo-epidemic in Central Europe and North America and, although rare (an
50 estimated incidence of 5.5 cases per million members of the age-related population), it is a major
51 public health concern [Ardissino *et al.*, 2016; Caprioli, 2005]. It is caused by zoonotic Shiga toxin-
52 producing *Escherichia coli* (STEC), which rarely cause disease in animals (although ruminants are
53 a major natural reservoir) [Caprioli, 2005] but typically reach humans as a result of food chain
54 contamination. However, the high prevalence of non-157 strains (less commonly found as
55 contaminants of the gut of ruminants compared to O:157 serotype) , the seasonal nature of the
56 disease (which is more frequent in the spring, summer and autumn), and its high incidence in rural
57 areas all suggest the possibility of other sources of transmission [Paton et al, 1998]. Furthermore,
58 the increasing number of unusual food vectors (such as vegetables) associated with human STEC
59 infection suggest the involvement of contamination, which may be significantly affected by local
60 meteorological conditions.

61 The seasonal nature of the disease is well documented [Riviero et al., 2012; Douglas and Kurien,
62 1997]. However, within the period of the year with higher incidence, affected children present in
63 clusters which are unrelated for spatially distant or for the disease is caused by different STEC
64 serotypes [Ardissino et al., 2003]. This finding (clusters, not epidemics) has suggested the possible
65 role of weather as a factor favouring the spread of the disease.

66 The aim of this study was to describe the relationship between STEC infection and weather
67 conditions because identifying the boundary conditions that increase the risk of infection may
68 provide important clues about sporadic cases of HUS and suggest new preventive strategies. This
69 was done by analysing the period from 2010 to 2013, which was characterised by important clusters
70 of infections in an area with a new monitoring network.

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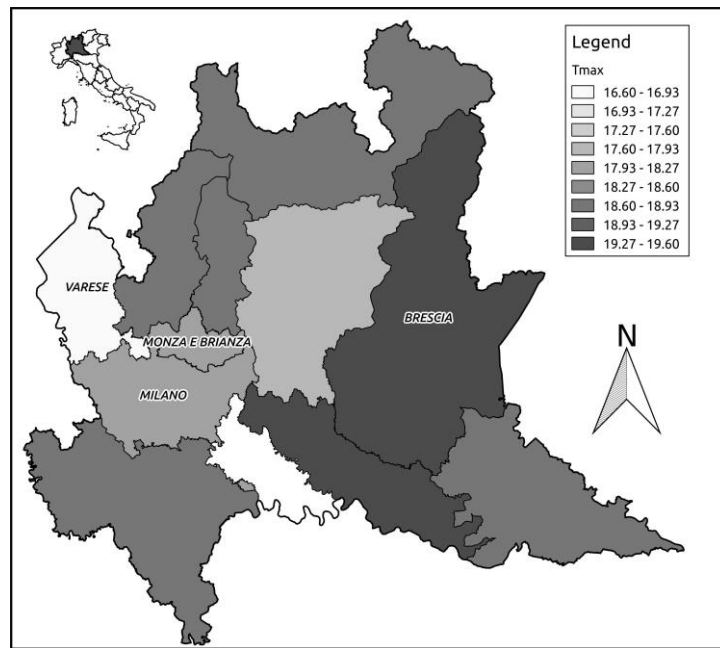
METHODS

Reference population and environment

The present study has considered the cases of STEC infections that have occurred in the Lombardy region, which in 2012 has an average under 21-year-old population of 1.9 million (as estimated by the Italian Institute of Statistics [ISTAT, 2012]). There are 0.57 million children in Milano, 0.16 million in Monza Brianza and Varese, and 0.25 million in Brescia..

Lombardy can be divided into three zones, city of Milano, the provinces of Varese, Como, Lecco, Monza, Brianza, Bergamo and Brescia and the provinces of Sondrio, Pavia, Cremona, Mantova and Lodi. In Milano the service sector makes up 65.3% of employment. The second is made up of a group of provinces which are highly industrialised but in Bergamo and Brescia, in the plains, are also constituted by a rich agricultural sector. Finally, the third group presents intensive agricultural activity.

The agriculture productivity in this region is enhanced by a well-developed use of fertilizers and an abundance of water. The productions in the higher plains include cereals, vegetables, fruit and mulberries but also the cattle (the highest density in Italy), pigs and sheep are bred and raised in this area.



92

93 **Figure 1:** Distribution of mean maximum annual temperature of Lombardy. The four study areas,
 94 Milano, Monza Brianza, Varese and Brescia are indicated by name.
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96

97 ***Data collection***

98 STEC dataset

99 The data used in this study were collected by the North Italian HUS (NI-HUS) network of 56
100 hospitals (pediatric units) coordinated by the Center for HUS Prevention, Control and Management,
101 Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy. The Center has been
102 operating in an area with 9.9 million inhabitants (1.9 million of pediatric age) since June 2010 with
103 the aim of implementing primary and secondary STEC-HUS prevention. The network's programme
104 includes the early diagnosis of STEC infection by rapidly screening the bloody diarrhea of under-
105 21-year-olds, defined as "diarrhea with visible blood in at least one bowel movement seen by health
106 professionals or reported by caregivers". Further details concerning the NI-HUS Network, its
107 procedures and organisational structure have been published elsewhere [Ardissino *et al.*, 2014].

108 The date of presumed infection in each case of bloody diarrhea positive for Stx 1 or Stx 2 was
109 estimated by subtracting 3 days from the onset of diarrhea (incubation period)..

110 The positive cases were then grouped on the basis of the province of residence in order to calculate
111 the monthly incidence rate using the age-related population as published in the 2012 census by the
112 Italian National Statistics Office (ISTAT), and the four provinces with the highest overall incidence
113 in the period 2010-2013 were selected: Milano (MI), Varese (VA), Monza Brianza (MB) and
114 Brescia (BS).

115 The study was approved by the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale
116 Maggiore Policlinico on 18 May 2010.

117 Meteorological data

118 The data concerning daily precipitation, minimum and maximum temperature, and minimum and
119 maximum relative humidity in the selected areas from 1999 to 2013 were recorded by the
120 Lombardy Regional Environmental Protection Agency (ARPA). The weather stations selected are
121 the most representative on the study area (Figure 1). This 15-year period was selected because it is

122 long enough to filter out any inter-annual variations or anomalies, but not too short to reveal
123 climatic trends [Storch and Zwiers, 2003]. The weather instruments in the Agency's automatic
124 stations are carefully calibrated once a year, and the daily data are subject to automatic checks that
125 allows them to be considered homogeneous: i.e. any variations are only due to variations in
126 climate [Conrad and Pollak, 1962; Peterson *et al.*, 1998; Aguilar *et al.*, 2003; Acquaotta *et al.*,
127 2009], thus reasonably excluding the possibility of systematic error.

128 ***Statistical analysis***

129 The climatic features of the study areas were defined by calculating rainfall, and the monthly
130 distribution of precipitation and temperatures. Climatograms associated with the corresponding
131 Peguy grids were used to classify the months as arid, warm temperate, cold or frosty and, on the
132 basis of the water supply, as hyper-humid, humid, sub-humid or dry. The thermograms showed
133 whether the main climate type was continental or temperate maritime. Finally, Balseinte polygons
134 were used to show the intensity of seasonal precipitation [Acquaotta and Fratianni, 2013].

135 The first relationships between the STEC and weather datasets were analysed using Spearman's
136 correlation coefficients calculated on a monthly scale as an independent, robust and resistant
137 method based on data ranks rather than the values themselves [Hauke and Kossowski, 2011].

138 Principal component analysis (PCA) of monthly series was used to identify closer relationships
139 between infection and weather variables. PCA is a statistical procedure that uses an orthogonal
140 transformation. The PCA turns into a fixed correlated variables in a set of linearly uncorrelated
141 variables, Principal Components (PC) [Venables and Ripley, 2002].

142 Each PC is calculated as:

$$143 \quad Y_i = l_{i1}X_1 + l_{i2}X_2 + \dots + l_{ip}X_p \quad \text{with } i = 1, 2, \dots, p$$

144 l_{ij} = weight of the variable (X_j)

145 Y_i is mainly characterized by X_j with greater l_{ij}

146 More information about the relationships between X_j and Y_i is added by their correlation coefficient

147 calculated by PCA.

148 $r_{(y_i, x_j)} = \text{Corr}(y_i, x_j) = e_{ij} \frac{\sqrt{\tau_i}}{\sigma_j}$; with e_{ij} eigenvector; τ_i eigenvalue; σ_j standard deviation

149 If we graphically consider a unit circle in the PC1 and PC2 plot, it is possible to represent the
150 correlation coefficients between X_j and Y_1 and between X_j and Y_2 . Each X_j variable is plotted inside
151 the unit circle with the following coordinates: $(\text{Corr}(Y_1, X_j), \text{Corr}(Y_2, X_j))$. In this way, a graphical
152 indication is given by the variables that determine the principal components, and their positive or
153 negative correlation is shown. Accordingly, if two variables show the same behavior with the PCs,
154 the results obtained from the correlation coefficient test are confirmed.

155 The daily datasets, estimated by subtracting 3 days from the onset of diarrhea (incubation period),
156 were also analysed in order to clarify the weather conditions favouring STEC infection. The
157 distributed lag non-linear model (DLNM) was used to examine the relationship between maximum
158 (minimum) temperature and daily illness during June 2010 to December 2013 [Bai *et al.*, 2014;
159 Cheong *et al.*, 2013; Gasparrini *et al.*, 2010] with a maximum lag of 30 days in order to ensure
160 greater coverage. The major advantage of this model is that it is able to describe a non linear
161 exposure–response association [Gasparrini, 2011; Gasparrini *et al.*, 2010]. Long-term trends were
162 controlled using a natural cubic spline with 7 df per year and the Day Of the Week (DOW) was also
163 included as an indicator in the analysis. The temperature and the lagged effects have been
164 represented by a natural cubic spline with 3 degrees of freedom. To select the adequate fit the
165 Akaike Information Criterion (AIC) was used [Akaike, 1973; Zhang *et al.*, 2014; Gasparrini, 2013].
166 The STEC dataset was also compared with five climate indices created by the Expert Team on
167 Climate Change Detection and Indices (ETCCDI) in order to highlight variations in extreme events
168 in the study: the frequency, amplitude, magnitude, number and duration of heat waves (HWs) (Tab.
169 1) [Fortin *et al.*, 2016; Peterson *et al.*, 2005, 2001; Karl *et al.*, 1999]. A HW for minimum
170 temperature, T_{\min} , or maximum temperature, T_{\max} , was defined as any period between May to
171 September with three or more days during which T_{\min} was $>90^{\text{th}}$ percentile of T_{\min} or T_{\max} was

172 >90th percentile of Tmax; the 90th percentiles were calculated over the reference period 2000-2010.

173 The linear regression between HW variables and infections was then calculated.

174 The trends were computed using the TheilSen approach (TSA) [Sen 1968; Zhang et al., 2000; Toreti

175 and Desiato, 2008, Acquaotta et al., 2015]. The trend is removed from the series if it is significant

176 and the autocorrelation is computed. The Mann-Kendall test for the trend is then run on the

177 resulting time series to compute the level of significance [Giaccone *et al.*, 2015].

178

179 **Table 1.** ETCCDI climate indices

ID	Indicator name	Definitions	UNIT
HWN	Heat wave number	The number of individual heat waves occurring each summer (May-September). A heatwave is defined as 3 or more days where Tmax > 90 th percentile of Tmax or where Tmin > 90 th percentile of Tmin. Where percentiles are calculated from base period specified by user	No. of events
HWD	Heat wave duration	The length of the longest heat wave identified by HWN.	days
HWF	Heat wave frequency	The number of days contributing to the heat waves identified by HWN	days
HWA	Heat wave amplitude	The peak day value of hottest heat wave (defined as the heat wave with highest HWM)	°C
HWM	Heat wave magnitude	The mean temperature of all heatwaves identified by HWN.	°C

180

181 **RESULTS**

182 A total of 53 STEC infections were identified in the selected areas between June 2010 and

183 December 2013; 5 of them only, turned into HUS. The vast majority of the infections occurred

184 between May and September. The highest incidence (19) was recorded in May-September 2011,

185 followed by the season 2013 (6). The month with the largest number of cases (10) was August 2011

186 (Fig. 2), during which the principal cluster of infections was also recorded (seven cases between 19

187 and 28 August). The second principal cluster occurred in September 2012 (three cases between 11

188 and 14 September).

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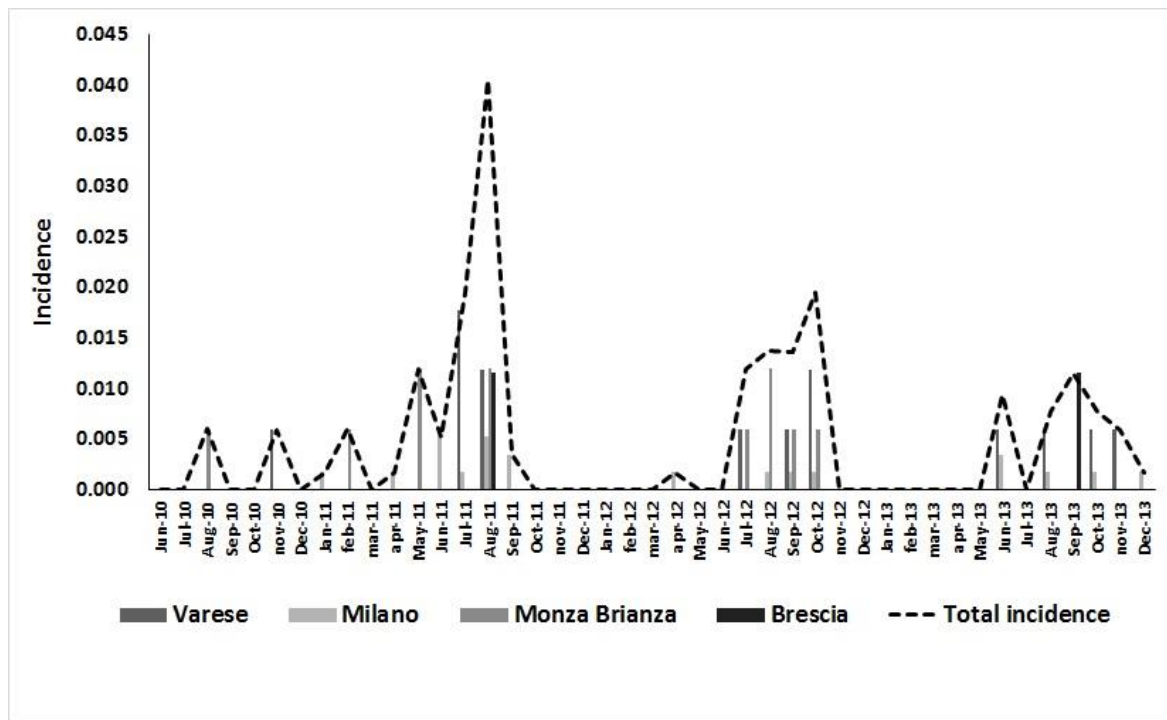


Figure 2. Incidence and timing of STEC infections in the study areas between June 2010 and December 2013.

The four study areas have a continental climate characterised by inter-annual temperature excursions, the largest being recorded during the summer and the smallest during the winter (Fig. 3). The majority of months are temperate and humid, but the winter months are as cold and humid or hyper-humid, and July and August as hot and humid or sub-humid. The mean temperatures between 1999 and 2013 ranged from 13.3°C (Varese) to 14.6°C (Milano); during May-September, the mean temperature ranged from 18.6°C (Varese) to 25.3°C (Brescia). Maximum temperatures were recorded during the month of July, followed by August. During May-September, the highest maximum temperature (39.4°C) was recorded in Brescia during July 2013, followed by Monza Brianza; the highest minimum temperature was recorded in Milano, followed by Monza Brianza. The behaviour of maximum and minimum humidity was similar in the four areas: Hmax was between 67% and 100%, and Hmin between 33% and 65%. The maximum mean relative humidity was recorded in the winter (92.6% in November), the mean minimum value in the summer (39.6% in July).

Mean annual precipitation ranged from 873.5 mm (Milano) distributed over 80 rainy days to 1456.4

208 mm (Varese) distributed over 94 rainy days. Maximum rainfall density was recorded during the
 209 autumn followed by the spring, with the highest levels being recorded in Varese (19.4 mm/day
 210 during autumn, followed by 14.7 mm/day in spring). Rainfall in Milano, Monza Brianza and Varese
 211 was sub-alpine (peaking in autumn with a secondary peak in spring, and minimum in winter); in
 212 Brescia, it was sub-continental with a maximum in autumn following by summer (Fig. 3).
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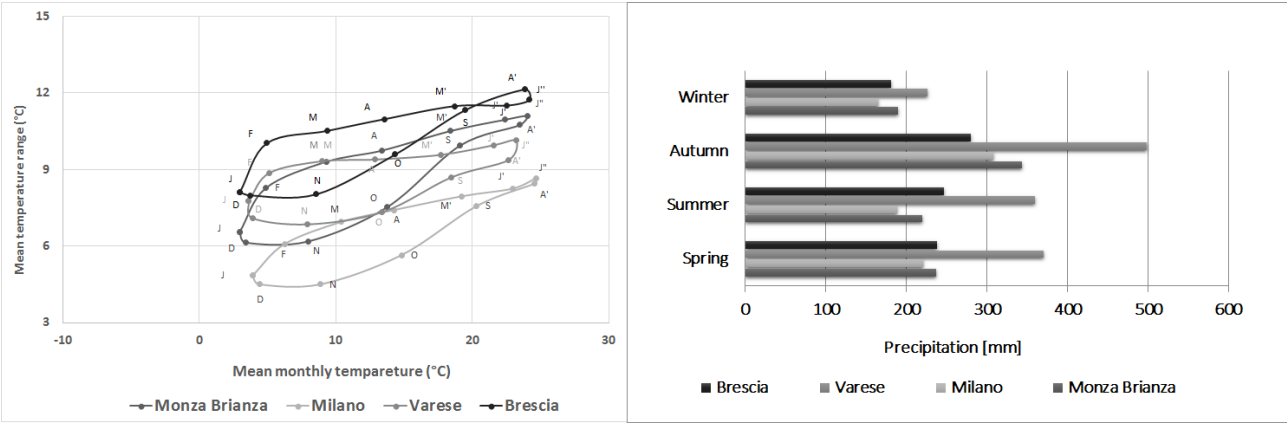


Figure 3. Left) Thermograms of the four areas. Right) Seasonal distribution of rainfall.

216 The analysis showed that Milano and Monza Brianza had the same climatic features, whereas
 217 Brescia was characterised by differences in temperature (+1.3°C in summer) and rainfall (greater in
 218 summer), and Varese by a difference in the amount of rainfall (+520 mm/year), but its distribution
 219 over the year was the same.

220 The correlation coefficients did not show any close relationships (maximum 0.36, minimum -0.36),
 221 although it was possible to identify a systematic relationship between STEC infections and the
 222 meteorological variables (Tab. 2). There was no statistically significant correlation in Brescia, but
 223 there were statistically significant correlations with maximum and minimum temperatures (but not
 224 precipitation) in Milano, Monza Brianza and Varese, and a statistically significant correlation with
 225 relative humidity, in Monza Brianza.

226
 227 **Table 2.** Correlation Coefficients, Corr Coeff, between STEC infections, meteorological variables,
 228 and principal and second components in the four areas. R: rainfall; Tmax: maximum temperature;
 229 Tmin: minimum temperature; Hmax: maximum relative humidity; Hmin: minimum relative

230 humidity; STEC: infection; PC1: principal component; PC2 second component. Statistically
 231 significant correlation coefficients: *90%, **95%.
 232

	Variable	PC1	PC2	Corr Coeff
Milano	STEC	-0.36	0.57	
	Tmax	-0.91	0.33	0.33**
	Tmin	-0.87	0.39	0.36**
	R	0.42	0.69	-0.1
	Hmax	0.90	0.34	-0.05
	Hmin	0.88	0.28	-0.09
Monza Brianza	STEC	0.51	0.34	
	Tmax	0.93	0.20	0.36**
	Tmin	0.86	0.29	0.34**
	R	-0.45	0.83	-0.02
	Hmax	-0.89	0.14	-0.26*
	Hmin	-0.92	0.12	-0.31*
Varese	STEC	-0.18	0.59	
	Tmax	-0.81	0.51	0.27*
	Tmin	-0.75	0.60	0.31**
	R	0.56	0.58	0.07
	Hmax	0.87	0.36	0.005
	Hmin	0.87	0.38	0.008
Brescia	STEC	0.23	-0.11	
	Tmax	0.93	0.27	0.23
	Tmin	0.87	0.37	0.21
	R	-0.21	0.92	-0.19
	Hmax	-0.82	0.31	-0.03
	Hmin	-0.90	0.10	-0.09

233

234 In all of the areas except Brescia, the correlation coefficients between the variables and the PCA

235 show a linear relationships between maximum and minimum temperature, STEC infections and the

236 principal and second components. The PCA plots (Fig. 4) show that the variables, Tmax, Tmin and

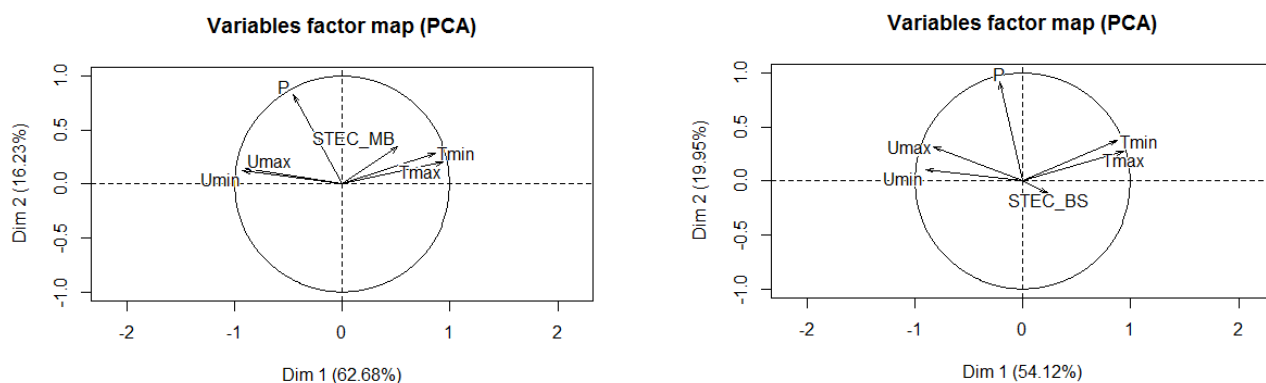
237 STEC, in the areas with the same climatic features (Milano, Monza Brianza and Varese) show the

238 same relationships with the PC1 and PC2 highlighting a close link between temperature and

239 infections. In Brescia, infections did not closely correlate with the principal components and

240 accordingly with the weather variables (Fig. 4).

241

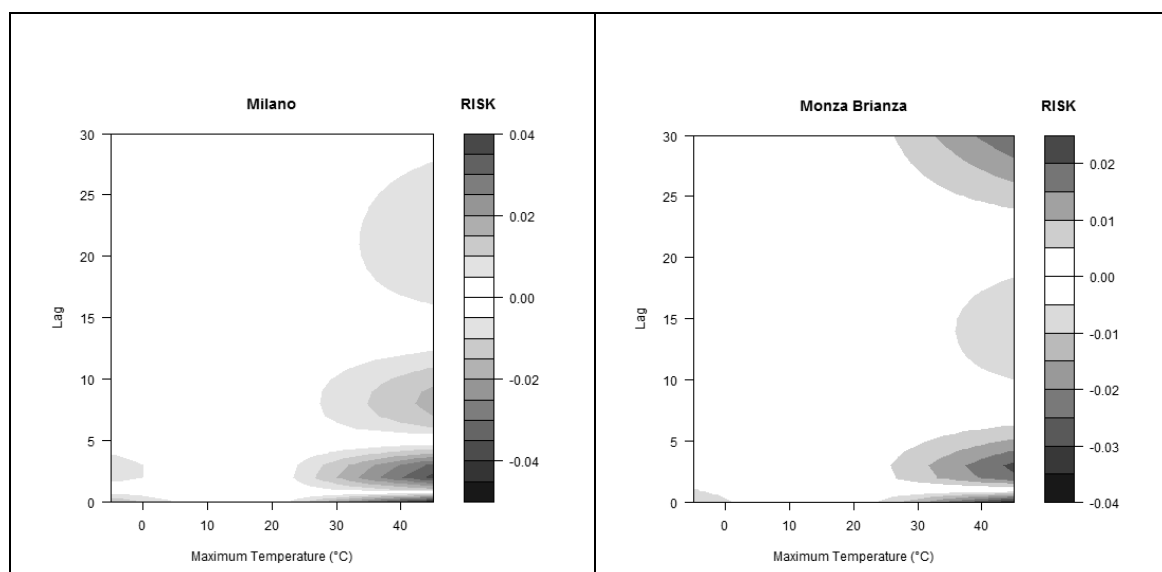


242 **Figure 4:** Correlation coefficient between the variables and the PC1 and PC2, Left) PCA of Monza
 243 Brianza. Right) PCA of Brescia.

244

245 On the basis of these results, we decided to use the DLNM only for the maximum and minimum
 246 temperature series. In Milano, Monza Brianza and Varese, the risk of infection was greater in the
 247 case of high maximum temperatures and lags of 0-5 days (the risk is greatest with three consecutive
 248 days of high temperatures); in Brescia, the risk increased on the same day as the increase in
 249 temperature (Fig. 5). The temperature threshold in each area was calculated as mean of 90th
 250 percentile estimated for every provinces (Table 3).

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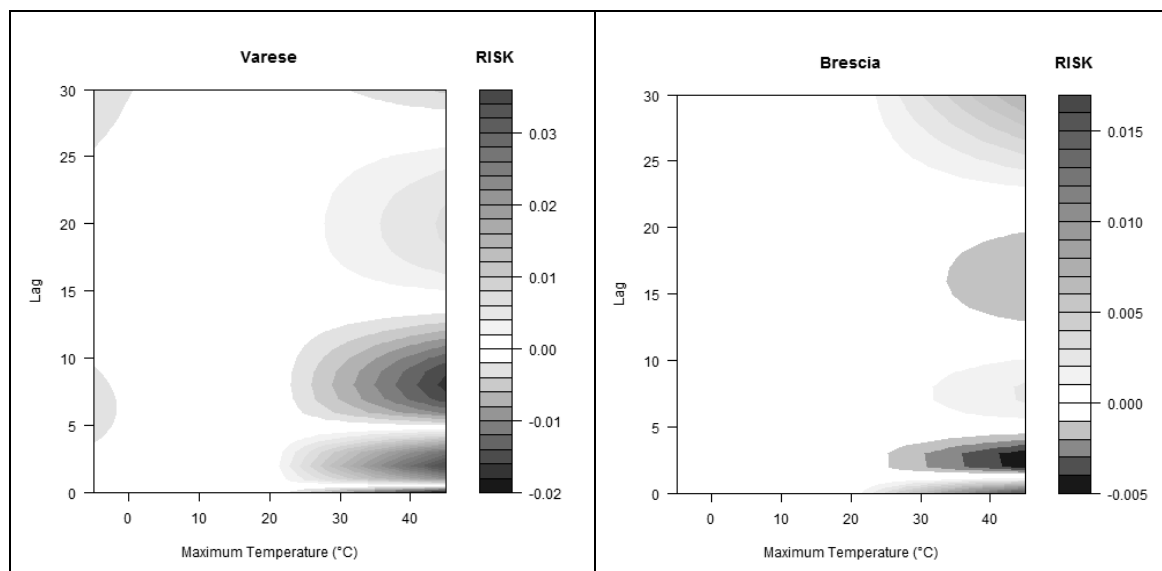


Figure 5: Relative risk of STEC infection by maximum temperatures. The column on the right indicates the risk of infection.

The number, maximum duration, amplitude, frequency and the mean maximum temperature of the heat waves in each area were calculated. Heat waves were defined as periods of three days or more during which Tmax was >90th percentile calculated for each area from May to September (Table 3). Table 4 shows that the year with the most heat waves was 2011: three heat waves in Milano for a total of 29 days, five in Monza Brianza for a total of 42 days, one in Varese for a total of 19 days, and six in Brescia for a total of 45 days. In the same year, the number of infections was at its highest in each area, particularly Milano (nine cases) and Varese (five cases). The principal cluster of infections occurred between 19 and 28 August 2011 (seven cases recorded in ten days: two each in Milano, Brescia and Varese, and one in Monza Brianza), and there was a heat wave in Lombardy from 17 to 26 August because of a strong North African anticyclone. The temperatures were higher than expected for the period. Rain was scarce with poor and irregular cumulative precipitation on the ground.

Table 3: 90th percentile calculated on the selected daily series from May to September and the mean value for the 90th percentile. The 90th percentiles were calculated over the reference period 2000-2010 month by month.

Month Tx90 th	Milano	Monza Brianza	Varese	Brescia
--------------------------	--------	---------------	--------	---------

May	25.8	27.9	24.5	29.2
June	30.3	31.7	28.6	33.1
July	31.5	32.9	30.4	33.4
August	32.7	33.7	29.9	34.0
September	28.2	28.7	25.7	28.5
Mean	29.7	30.9	27.8	31.6

Table 4. The number of infections (STEC), heat wave magnitude (HWM), heat wave amplitude (HWA), heat wave number (HWN), heat wave duration (HWD) and heat wave frequency (HWF) from May to September calculated for each areas.

	Period (May-Sept)	STEC	HWM	HWA	HWN	HWD	HWF
MILANO	2010	0	//	//	0/	//	//
	2011	9	30.6	36	3	10	29
	2012	2	34.0	34.8	1	3	3
	2013	3	34.0	34.4	1	5	5
MONZA BRIANZA	2010	1	33.1	33.7	1	3	3
	2011	4	30.4	36.3	5	16	42
	2012	4	31.5	36.8	3	11	17
	2013	0	34.6	35.3	1	5	5
VARESE	2010	0	31.0	31.8	1	4	4
	2011	5	28.8	32.4	1	19	19
	2012	2	29.3	33	2	6	9
	2013	2	31.3	32.8	3	4	11
BRESCIA	2010	0	32.9	33.2	1	3	3
	2011	3	31.8	37.6	6	16	45
	2012	0	33.7	38.3	6	9	31
	2013	3	36.3	39.4	3	7	15

A second principal cluster was recorded from 11 to 14 September 2012 (three cases: one in Milano, one in Monza Brianza, and one in Varese), and was once again associated with a heat wave. Temperatures gradually increased from 3 to 11 September (maximum temperatures were 2-3°C higher than the mean, particularly between September 7 and 9), and rain was relatively scarce. The trends between the STEC incidences and monthly heat waves from May to September (Table 5) show a statistically significant slopes only in 5 cases, 2 cases in Milano (HWN and HWD) and 3 cases in Monza Brianza (HWN, HWD and HWF) The maximum trend, 0.003 incidence/number of HW, is calculated for the number of heat waves in Monza Brianza following by the trend of the

number of heat waves, 0.002 incidence/number of HW, calculated in Milano. Independently by the statistically significant of the trends, the relationships between the STEC incidences and the monthly HW were the same in the three areas with the same climatic features (Milano, Monza Brianza and Varese). In these areas the trends highlight a linear relationships with number, duration, amplitude and magnitude of heat waves and STEC incidences confirming the results by the DLNM where the risk of infections in these zones increases with the increase of the consecutive days classified hot, days with maximum temperature > 90th percentile.

In Brescia the trends are not statistically significant and the slopes are near to zero. The maximum value, 0.0001 incidence/(°C), is calculated for the amplitude of the heat waves while the minimum value, -0.0003 incidence/(°C), for the magnitude of heat waves. For this area there is not a linear relationships between STEC incidences and the heat waves as underline by correlation coefficient and PCA.

Table 5: Linear relationships between STEC infection incidence and monthly heat wave, heat wave magnitude (HWM), heat wave amplitude (HWA), heat wave number (HWN), heat wave duration (HWD) and heat wave frequency (HWF). The statistically significant relationships are in bold.

	HWM	HWA	HWN	HWD	HWF
Milano	//	0.0003	0.002	0.0004	//
Monza Brianza	0.001	0.0006	0.003	0.001	0.0001
Varese	0.0001	0.0004	0.001	//	//
Brescia	-0.0003	0.0001	-0.0001	//	//

DISCUSSION

The increase in the number of sporadic cases of STEC infections during particular periods of the year and in particular areas of the country has induced researchers to study possible relationships with local factors. The aim of the present study was to examine in detail the possible relationship between STEC infection and local weather conditions, a factor that has not been studied before and that could explain some of the epidemiological features of the disease and of its severe consequences.

309 The analysis of climate showed that Milano, Monza Brianza and Varese have similar climatic
310 features with the same annual distribution of temperatures and rainfall: mean annual temperatures
311 during the study period ranged from 13.3°C in Varese to 14.6°C in Milano, and rainfall was sub-
312 alpine with a primary peak in autumn and a secondary peak in spring. Brescia was different insofar
313 as it was 1.3°C warmer during the season May-September, and rainfall was sub-continental
314 (maximum in autumn, followed by summer).

315 The analysis of STEC infections in relation with climate showed that the increase in incident cases
316 is associated with heat waves (periods of three or more days during which maximum temperatures
317 are higher than the 90th percentile of the values measured from May to September). The duration,
318 magnitude, amplitude, number and frequency of heat waves had a positive linear correlation with
319 detected STEC infections.

320 It can be speculated that climate can favour disease spreading by several possible means. Firstly the
321 temperature can influence the proliferation of pathogens as well as its persistence in the
322 environment increasing its probability of encountering the host. In addition climate has an impact
323 on vectors (flies) and consequently on diseases spread by vectors. Finally, climate modifies human
324 activities and recreation therefore introducing risks which might not be as present with cooler
325 temperature.

326 The analyses of weather trends in Italy show an increasing temperatures, with more frequent
327 extreme values [Colombo *et al.*, 2016; Garzena *et al.*, 2015; Toreti *et al.*, 2008]. Over a 15 years
328 from 1999 to 2013, the 90th percentiles of both Tmax and Tmin increased in the studied areas, thus
329 seeming to indicate a gradual increase in the climatic conditions favouring STEC infections. As it is
330 likely that this trend will continue the near future, it can be assumed that there will be a gradual
331 increase in the risk of STEC infections

332

333 **CONCLUSIONS**

334 The findings of this study fill a gap in our knowledge of the possible role of climate in spreading

335 STEC infection which, although preventable, is still the leading cause of acute kidney injury in
336 children. Identifying the boundary weather conditions that favour the spread of the disease and their
337 evolution in the near future will enable more stringent controls in specific periods, thus favouring
338 early diagnosis and thereby reducing the severity of the disease and the related mortality.

339

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